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| APPLICATION NO.  | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|---------------------|------------------|
| 10/662,808   | 09/16/2003  | Sylvie Roux          | 03495.0174-02000    | 2497             |
| 22852 7590 01/29/2009<br>FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER<br>LLP<br>901 NEW YORK AVENUE, NW<br>WASHINGTON, DC 20001-4413 |             |                      |                     |                  |
| EXAMINER<br>CHEN, SHIN LIN   |             |                      |                     |                  |
| ART UNIT   |             | PAPER NUMBER         |                     |                  |
| 1632   |             |                      |                     |                  |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/662,808

**Applicant(s)**

ROUX ET AL.

**Examiner**

Shin-Lin Chen

**Art Unit**

1632

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 28 October 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 32, 33 and 68-92 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 32, 33 and 68-92 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/S5108)  
Paper No(s)/Mail Date 10-28-08
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Applicants' amendment filed 10-28-08 has been entered. Claim 32 has been amended. Claims 74-92 have been added. Claims 32, 33 and 68-92 are pending and under consideration.

#### ***Claim Rejections - 35 USC § 112***

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 80-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' amendment filed 10-28-08 necessitates this new ground of rejection.

The phrase "may be administered before, after, or simultaneously" in newly added claim 80 is vague and renders the claim indefinite. The phrase "may be" is an uncertain language. It is unclear whether the limitation after the phrase "may be" is intended in the claim or not. Claims 81-92 depend from claim 80 but fail to clarify the indefiniteness.

#### ***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 32, 33 and 68-73 remain rejected and the newly added claims 74-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stoop et al., 1996 (The Journal of Neuroscience, Vol. 16, No. 10, p. 3256-3264) in view of Miana-Mena et al., 2002 (PNAS, Vol. 99, No. 5, p. 3234-3239) and Poo, M-M., 2001 (Nature Review, Neuroscience, Vol. 2, p. 24-32) and is repeated for the reasons set forth in the preceding Official action mailed 4-29-08. Applicant's arguments filed 10-28-08 have been fully considered but they are not persuasive.

Claim 32 has been amended to specify "increasing the transport in a neuron". The newly added claims 74-92 specify injection into the LAL muscle or gastrocnemius muscle and tetanus toxin or its fusion protein is administered before, after, or simultaneously with the administration of BDNF, NT-4 or GDNF.

Applicants argue that the claims recite BDNF, GDNF and NT-4 but not NGF, NT-3 or CNTF and none of the cited references suggest that only GDNF, NT-4 and CNTF exhibit the claimed property. Applicants further argue that Stoop groups all of the neurotrophic factors together as if they all have the same activity and reports that CNTF and NT-3 have similar potentiation effects. Stoop does not teach that BDNF, NT-4 and GDNF but not NGF, NT-3 or CNTF increases transport as claimed (amendment, p. 9-10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-29-08. Stoop groups

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neurotrophic factors together to provide a general statement regarding the function of the neurotrophic factors. However, Stoop reports “differential and synergistic effects of brain-derived neurotrophic factor and ciliary neurotrophic factor” (see Title). Stoop teaches extracellular application of brain-derived neurotrophic factor (BDNF) to developing neuromuscular junctions in *Xenopus* nerve-muscle cultures resulted in an increase in the frequency of spontaneous synaptic currents and the amplitude of nerve-evoked synaptic current, and an increase in presynaptic cytosolic  $Ca^{2+}$ . The mechanism of CNTF on an increase in the frequency of spontaneous synaptic currents is different from that of BDNF. They have differential effects on the secretory machinery. Since neurotrophin BDNF can increase the frequency of spontaneous synaptic currents and the amplitude of nerve-evoked synaptic current, and increase presynaptic cytosolic  $Ca^{2+}$  concentration, and Miana-Mena teaches that intracellular and transneuronal traffics of TTC-LacZ fusion protein strongly depend on presynaptic neural cell activity, one of ordinary skill in the art would find it obvious to use BDNF to increase neuronal transport of tetanus toxin or TTC fusion protein. It would be obvious to one of ordinary skill in the art to administer the tetanus toxin or its fusion protein before, after, or simultaneously with the administration of the BDNF, NT-4 or GDNF because they are routine determination to optimize the effect of the neurotrophic factor on the neuronal transport of the tetanus toxin or its fusion protein in a neuron. It also would have been obvious for one of ordinary skill in the art to inject neurotrophic factor into Levator auris longus (LAL) muscle or gastrocnemius muscle because intramuscular injection of tetanus toxin or other protein to study retrograde axonal transport and transsynaptic transfer is well known in the art.

Applicants argue that Poo and Miana-Mena do not specify BDNF, NT-4 and GDNF that have ability to increase the internalization of the tetanus toxin or fusion protein as claimed and there is no predictable success with any given neurotrophin (amendment, p. 11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-29-08 and the reasons set forth above. Although Poo and Miana-Mena does not specify the claimed BDNF, NT-4 and GDNF, Stoop specifies extracellular application of brain-derived neurotrophic factor (BDNF) to developing neuromuscular junctions in *Xenopus* nerve-muscle cultures resulted in an increase in the frequency of spontaneous synaptic currents and the amplitude of nerve-evoked synaptic current, and an increase in presynaptic cytosolic  $Ca^{2+}$ . One of ordinary skill in the art at the time of the invention would find it obvious that BDNF would be able to increase the neural transport of tetanus toxin or tetanus toxin fusion protein in a neuron with reasonable expectation of success in view of the teachings of Stoop, Poo and Miana-Mena.

### ***Priority***

The subject matter of the instant invention, i.e. a method of modulating the transport in a neuron of a tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin by using BDNF, NT-4 or GDNF in vitro or in vivo, has not been disclosed by Application Nos. 09/816,467, 09/129,368, 60/055,615 and 60/065,236. Therefore, the claimed priorities of those applications set forth above are NOT granted. The effective filing date of the instant invention is the filing date of the instant application, i.e. 9-16-03.

Applicants argue that benefit of each of those applications has been claimed and each of those applications has been incorporated by references in their entities (amendment, p. 12). This

is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-29-08. The instant application is a continuation-in-part of Application No. 09/816,467, filed 3-26-01. The subject matter of the instant invention, i.e. a method of increasing the transport in a neuron of a tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin by using BDNF, NT-4 or GDNF in vitro or in vivo, has not been disclosed by Application Nos. 09/816,467, 09/129,368, 60/055,615 and 60/065,236. Therefore, the claimed priorities of those applications set forth above are NOT granted.

### *Conclusion*

No claim is allowed.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

/Shin-Lin Chen/  
Primary Examiner, Art Unit 1632